**REMARKS**

In the Office Action of December 12, 1997, the Examiner has rejected claims 2, 5, 6, 8, and 10-12, objected to claims 7 and 9 and withdrawn claim 1, 3, and 4 from consideration. In this amendment, applicants amend claim 5 and add claim 13. As such claims 1-13 are pending for examination. Support for the amendment to claim 5 is found, for example, on pages 12-15 which discuss recombinant production of human PAP and pages 15-17 which discuss dephosphorylation of a substate. Support for claim 13 is found in orginally filed claim 10.

**I. Election With Traverse**

Applicants acknowledge that during a telephone conversation on October 30, 1997, applicants' representative elected claims 2 and 5-12 with traverse. Applicants' reason for traverse is that it would not present an undue burden for the Examiner to consider the non-elected claims along with the elected claims.

**II. §102 Rejection Over Boder *et al.***

The Examiner has rejected claims 5, 10, and 11 as anticipated by Boder *et al.*, *Cellular Signalling* 6:933-41 (1994). Claim 5, as amended, recites a step of "recombinantly producing a human phosphatidic acid phosphatase protein." This step is neither taught or suggested by the Boder reference. Accordingly, applicants respectfully request that the Examiner withdraw the rejection of claims 5, 10, and 11 over the Boder reference. Furthermore, applicants maintain that added claim 13 is not anticipated by Boder *et al.* because, *inter alia*, Boder does not disclose the substrates recited in claim 13.

**III. §103 Rejection Over Kai *et al.* In View of Genbank Entries AA040858, W04968, and H68363**

The Examiner has rejected claims 2, 5, 6, and 10-12 as obvious over Kai *et al.*, *J. Biol. Chem.* 271:18931-38 (1996) in view of Genbank Entries AA040858, W04968, and H68363. Applicants respectfully traverse.

A. Claims 5 and 10-12

Applicants maintain that the cited Genbank entries do not render obvious claims 5 and 10-12. Applicants note that the Genbank entries are Expressed Sequence Tags (ESTs), and in particular, the cited entries are cDNA sequence fragments that have been randomly sequenced from the 3' (the polyadenylation tail) end of a transcript derived from a human cDNA library of various tissues. The Genbank entries describe no putative start codon, stop codon or function to the perspective sequences. As such, the cited ESTs would not have lead the skilled artisan to believe that the cited fragments encoded any particular protein. In fact, it is often the case that ESTs do not contain any coding sequences but only list regulatory sequences. Accordingly, applicants believe that the cited ESTs fail to teach or suggest the claimed human phosphatidic acid phosphatase protein (hereinafter "human PAP protein").

Furthermore, applicants respectfully traverse the Examiner's assertion that the cited homology between the Genbank entries and the murine and porcine sequences of the Kai reference would have rendered obvious the subject matter of claims 5 and 10-12. Specifically, the Examiner has stated that "it would have been obvious to one of ordinary skill in the art [based on the cited homology] that there is a human homolog of the PAP of Kai *et al*. which is highly homologous to the mouse and porcine proteins." Applicants respectfully disagree and submit that the existence of a cDNA fragment with homology to the Kai sequence would not have indicated the existence of a full length functional human PAP protein.

B. Claims 2 and 6

Applicants traverse the Examiner's rejection of claims 2 and 6 for the same reasons given above. Moreover, applicants believe claims 2 and 6 are further patentable for the following reasons. Applicants submit that the Federal Circuit has emphasized the importance of structural obviousness in establishing a case of *prima facie* obviousness of DNAs and amino

acids. In particular, in *In re Deuel*, 51 F.3d 1552, 1558, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995) the court noted "Normally, a *prima facie* case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound." In particular, the court held that the prior art teaching of a 19 amino acid N-terminal sequence did not render obvious claims to particular DNAs because "one could not have conceived the subject matter of claims 5 and 7 based on the teachings in the cited prior art because, until the claimed molecules were actually isolated and purified, it would have been highly unlikely for one of ordinary skill in the art to contemplate what was ultimately obtained. *What cannot be contemplated or conceived cannot be obvious.*" *Id.* (emphasis added).

Applicants maintain that the holding of *In re Deuel* governs in the instant situation. That is, the cited fragment cannot render obvious claims directed to specific full-length amino acid sequences because the skilled artisan could not have contemplated the remaining amino acids. As stated by the court, "[w]hat cannot be contemplated or conceived cannot be obvious." Moreover, applicants submit that the teachings of the Kai reference do not remedy this defect in the cited Genbank entries.

**III. §103 Rejection Over Kai *et al*. In View of Genbank Entry U79294**

The Examiner has rejected claims 5, 8 and 10-12 as obvious over the Kai reference in view of Genbank Entry U79294. The Examiner maintains that "In view of the sequence identity between the cDNA of GENBANK entry U79294 and the mouse PAP cDNA of Kai et al., it would have been obvious to one of ordinary skill in the art that the cDNA disclosed by GENBANK entry U79294 encodes a human PAP." Specifically, the Examiner states that the cDNA of the cited entry "is identical to bases 225-1362 of SEQ ID NO:6 [sic; SEQ ID NO:5] (except for a single base deletion which is virtually certainly a sequencing error and not an actual difference in the nucleotide sequence) encompassing all of the

coding sequence of SEQ ID NO:5. This cDNA also exhibits 62% sequence identity with the mouse cDNA encoding PAP of Kai *et al.*"

A. Claims 5, and 10-12

With regard to claims 5 and 10-12, applicants submit that the cited Genbank entry does not suggest a human PAP protein, but in fact teaches away from such a protein. Applicants submit that the cited Genbank entry discloses a nucleic acid sequence encoding a putative protein having a stop codon at position 234. (Applicants include herein as ATTACHMENT A an amino acid comparison of the cited Genbank entry and the amino acid sequence encoded by SEQ ID NO:5 as well as a nucleic acid sequence comparison; the Examiner will note that the putative sequence of the cited Genbank entry contains a stop codon (*) at amino acid position 234.)

Applicants submit that the skilled artisan without knowledge of applicants' disclosed sequence would have assumed the fidelity of the cited Genbank entry. As such, the skilled artisan would have believed that the protein encoded by Genbank reference was 234 amino acids in length based on the stop codon at this position. Accordingly, applicants submit that the skilled artisan, being unaware of the sequences discovered by the instant inventors would not have concluded, as did the Examiner, that the stop codon at position 234 results from "virtually certainly a sequencing error."

In this vein, applicants submit that the putative 234 amino acid sequence of the cited Genbank entry when compared to the considerably longer deduced 283 amino acid sequence disclosed by the Kai reference would have lead the skilled artisan to believe that the cited Genbank entry did not encode human PAP. Applicants see no reason, and the Examiner has provided no reason, why the skilled artisan would have disregarded the actual sequence disclosed in the Genbank entry and the existence of a stop codon at position 234.

Applicants submit that a 62% homology standing alone would not lead a skilled artisan to believe that the cited Genbank

entry represented a homologue of the sequence disclosed by the Kai reference. Specifically, whether a specific percentage of sequence identity would lead the skilled artisan to believe that an unidentified sequence represents a homologue of a known sequence depends on an examination of the specific regions of homology and a determination of whether these regions are believed to represent conserved sequences that would indicate a species homologue. The Examiner, however, has provided no teaching in the art that the regions representing the 62% identity would have led the skilled artisan to believe that the cited Genbank sequence is a human homologue of the murine sequence disclosed by the Kai reference.

Moreover, even if the art would have led the skilled artisan to believe that the Genbank sequence might be a homologue to the Kai murine sequence, in the eyes of the law this would have only represented, at most, an invitation to experiment, which is insufficient support for an obviousness rejection. Applicants submit that a *prima facie* showing of obviousness requires a showing of likelihood of success, and applicants submit that the Examiner's citation of a 62% identity does not satisfy this requirement. Specifically, applicants point out that it was not known at the time of the filing of this application the degree of homology that a human PAP protein would exhibit when compared to the murine variety of the enzyme.

In fact, applicants submit that the lack of predictability inherent in using the disclosed murine sequence to gauge the existence of a human homologue is evidenced by the fact that the Kai reference disclosed a single PAP protein. In contrast, the present inventors have found that human PAP exists in at least four isoforms, denominated by the inventors as PAP-$\alpha$(1 and 2), PAP-$\beta$ and PAP-$\gamma$.

Given the teaching of the Kai reference, the skilled artisan would have believed that human PAP existed as a single isoform, when in fact, there are at least four different isoforms of PAP which are expressed by humans. Applicants believe that this discrepancy evidences that a homology of 62% between the

cited Genbank entry and the Kai murine sequence would not have suggested with a reasonable likelihood of success that the cited Genbank entry encodes a human PAP protein that could be used for dephosphorylating a substrate.

B. Claim 8

With regard to claim 8, applicants submit that this claim is further patentable because the cited references do not teach the specific amino acids claimed for the reasons mentioned above.

**V. Conclusion**

In view of the above remarks and amendments, applicants believe this application to be in condition for allowance and such a Notice is respectfully requested.

Respectfully submitted,

March 3, 1998
Date

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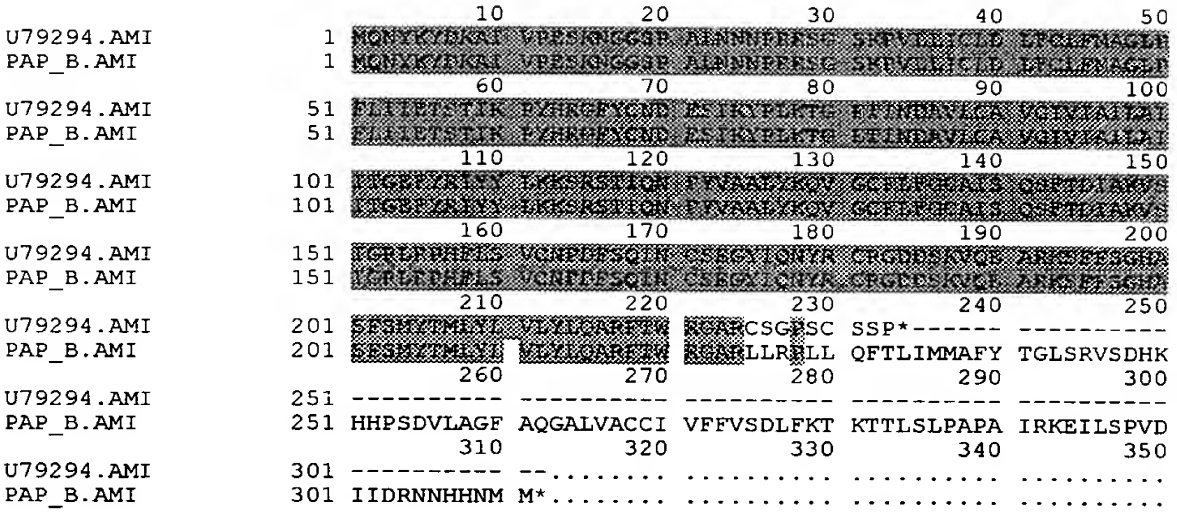
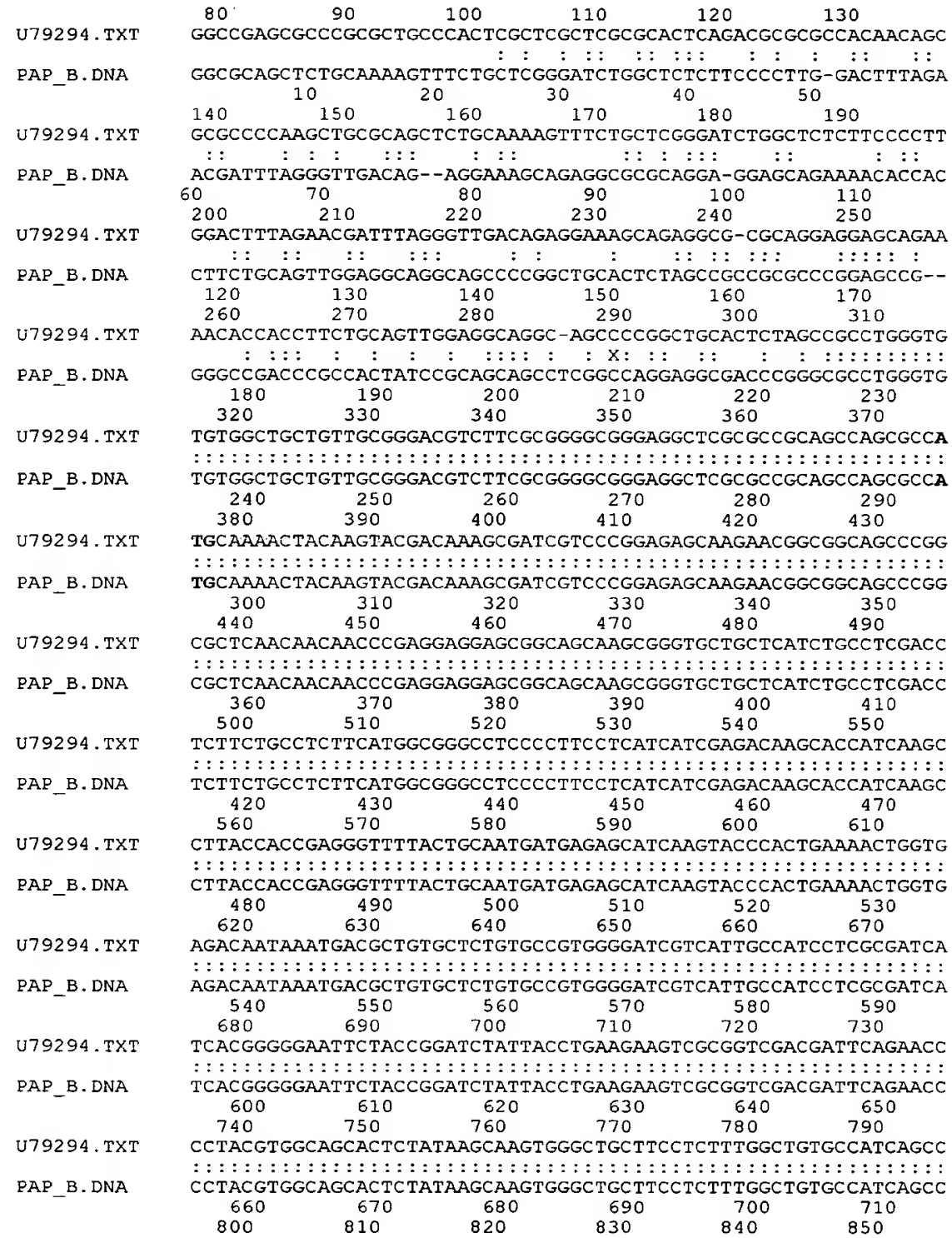
**Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.**

Comparison of Genbank U79294 to Cti human PAP-β



Comparison of full DNA sequence of Genbank U79294 and Cti human PAP-β



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U79294.TXT    AGTCTTTCACAGACATTGCCAAAGTGTCCATAGGGCGCCTGCGTCCTCACTTCTTGAGTG
              ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
PAP_B.DNA     AGTCTTTCACAGACATTGCCAAAGTGTCCATAGGGCGCCTGCGTCCTCACTTCTTGAGTG
                 720       730       740       750       760       770
               860       870       880       890       900       910
U79294.TXT    TCTGCAACCCTGATTTCAGCCAGATCAACTGCTCTGAAGGCTACATTCAGAACTACAGAT
              ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
PAP_B.DNA     TCTGCAACCCTGATTTCAGCCAGATCAACTGCTCTGAAGGCTACATTCAGAACTACAGAT
                 780       790       800       810       820       830
               920       930       940       950       960       970
U79294.TXT    GCAGAGGTGATGACAGCAAAGTCCAGGAAGCCAGGAAGTCCTTCTTCTCTGGCCATGCCT
              ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
PAP_B.DNA     GCAGAGGTGATGACAGCAAAGTCCAGGAAGCCAGGAAGTCCTTCTTCTCTGGCCATGCCT
                 840       850       860       870       880       890
              980       990      1000      1010      1020      1030
U79294.TXT    CCTTCTCCATGTACACTATGCTGTATTTGGTGCTATACCTGCAGGCCCGCTTCACTTGGC
              ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
PAP_B.DNA     CCTTCTCCATGTACACTATGCTGTATTTGGTGCTATACCTGCAGGCCCGCTTCACTTGGC
                 900       910       920       930       940       950
              1040      1050      1060      1070      1080      1090
U79294.TXT    GAGGAGCCCG▒CTGCTCCGGCCCCTCCTGCAGTTCACCTTGATCATGATGGCCTTCTACA
              :::::::::: ::::::::::::::::::::::::::::::::::::::::::::::::
PAP_B.DNA     GAGGAGCCCG▒CTGCTCCGGCCCCTCCTGCAGTTCACCTTGATCATGATGGCCTTCTACA
                 960       970       980       990      1000      1010
              1100      1110      1120      1130      1140      1150
U79294.TXT    CGGGACTGTCTCGCGTATCAGACCACAAGCACCATCCCAGTGATGTTCTGGCAGGATTTG
              ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
PAP_B.DNA     CGGGACTGTCTCGCGTATCAGACCACAAGCACCATCCCAGTGATGTTCTGGCAGGATTTG
              1020      1030      1040      1050      1060      1070
              1160      1170      1180      1190      1200      1210
U79294.TXT    CTCAAGGAGCCCTGGTGGCCTGCTGCATAGTTTTCTTCGTGTCTGACCTCTTCAAGACTA
              ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
PAP_B.DNA     CTCAAGGAGCCCTGGTGGCCTGCTGCATAGTTTTCTTCGTGTCTGACCTCTTCAAGACTA
              1080      1090      1100      1110      1120      1130
              1220      1230      1240      1250      1260      1270
U79294.TXT    AGACGACGCTCTCCCTGCCTGCCCCTGCTATCCGGAAGGAAATCCTTTCACCTGTGGACA
              ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
PAP_B.DNA     AGACGACGCTCTCCCTGCCTGCCCCTGCTATCCGGAAGGAAATCCTTTCACCTGTGGACA
              1140      1150      1160      1170      1180      1190
              1280      1290      1300      1310      1320      1330
U79294.TXT    TTATTGACAGGAACAATCACCACAACATGATGTAGGTGCCACCCACCTCCTGAGCTGTTT
              ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
PAP_B.DNA     TTATTGACAGGAACAATCACCACAACATGATGTAGGTGCCACCCACCTCCTGAGCTGTTT
              1200      1210      1220      1230      1240      1250
              1340      1350      1360      1370      1380      1390
U79294.TXT    TTGTAAAATGACTGCTGACAGCAAGTTCTTGCTGCTCTCCAATCTCATCAGACAGTAGAA
              ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
PAP_B.DNA     TTGTAAAATGACTGCTGACAGCAAGTTCTTGCTGCTCTCCAATCTCATCAGACAGTAGAA
              1260      1270      1280      1290      1300      1310
              1400      1410      1420      1430      1440
U79294.TXT    TGTAGGGAAAAACTTTTGCCCGACTGATTTTTAAAAAAAAAAAAAAAA
              ::::::::::::::::::::::::::::::::::::::::::::::::v
PAP_B.DNA     TGTAGGGAAAAACTTTTGCCCGACTGATTTTTAAAAAAAAAAAAAAAA
              1320      1330      1340      1350      1360
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